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EXAMINER	
HOWARD, ZACHARY C	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,090	FERGUSON, DUNCAN C.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,9,13,34-38,59-63,65,70,72-75,77-83 and 85-98* is/are pending in the application.

4a) Of the above claim(s) *86,94 and 95* is/are withdrawn from consideration.

5)☒ Claim(s) *2,3,34-36,59,60,70,72,81-83,85,87,88,90-92 and 96-98* is/are allowed.

6)☒ Claim(s) *13,37,38,61,62,73,75,79,80,89 and 93* is/are rejected.

7)☒ Claim(s) *9,13,63,65,73-75,77-79,89 and 93* is/are objected to.

8)☒ Claim(s) *See Continuation Sheet* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims subject to restriction and/or election requirement are 2,3,9,13,34-38,59-63,65,70,72-75,77-83 and 85-98.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 4/17/09 has been entered in full. Claims 2, 3, 9, 13, 34, 37, 59, 61-63, 65, 70, 72-75, 77, 79, 81-83 and 86 are amended. Claims 1, 4, 5, 55-58, 64, 66-69, 71, 76 and 84 are canceled (claims 6-8, 10-12, 14-33, 39-54 were canceled previously). New claims 87-98 are added.

Claims 2, 3, 9, 13, 34-38, 59-63, 65, 70, 72-75, 77-83 and 85-98 are pending.

Election/Restrictions

In view of Applicant's amendments to the claims, all claims directed to the elected species of polypeptide (isolated thyrotropin β-subunit) are now allowable. As such, claims previously withdrawn as directed to a non-elected species of polypeptide (yoked polypeptides comprising isolated thyrotropin β-subunit and thyrotropin α-subunit) are herewith rejoined and are subject to examination (claims 9, 13, 37, 38, 62, 63, 65, 73-75 and 77-80). Applicant's arguments (pg 11; 4/17/09) that the species election was an improper "restriction between combination and subcombination inventions" are moot in view of the rejoinder of the claims directed to the non-elected species.

At page 10 of the 4/17/09 response, Applicant traverses the restriction requirement, arguing that the amended claims now all possess the same special technical feature ("comprise SEQ ID NO: 1").

This argument has been fully considered and is found persuasive. Applicant's amendments to the claims result in the claims being limited to a special technical feature ("comprise SEQ ID NO: 1"). Therefore, pursuant to 37 C.F.R. 1.475 (B-D), the ISA/US considers that where multiple products and processes are claimed, the main invention shall consist of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly, the main invention (Group I) now comprises the first product (a polypeptide comprising SEQ ID NO: 1 and compositions and kits comprising said polypeptides; claims 2, 3, 9, 13, 37, 38, 59-63, 65, 70, 72-75, 77-83, 85, 87-93 and 98), the method of

making this product (including polynucleotides encoding said polypeptides; claims 96 and 97), and the first recited method of use of this product (a method of treating hyperthyroidism comprising administering a polypeptide; claims 34-36).

Thus, this application now contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I, claims 2, 3, 9, 13, 34-38, 59-63, 65, 70, 72-75, 77-83, 85, 87-93 and 96--98, drawn to a polypeptide, compositions and kits comprising said polypeptide, a polynucleotide encoding said polypeptide and a method of treating hyperthyroidism comprising administering said polypeptide.

Group II, claim 86, drawn to a method of making an antibody comprising immunizing an animal with a feline thyrotropin β-subunit.

Group III, claim 94, drawn to an isolated antibody.

Group IV, claim 95, drawn to a method of detecting a thyrotropin polypeptide in a sample using an antibody.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Groups II and IV do not share the same or corresponding technical feature because the methods of Groups II and IV are not coextensive with the methods of Group I and each of the methods has different method steps and goals. Furthermore, Group IV is a method of using a different product (antibody) from that of Group I. As noted above, the main invention consists only of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto.

Group III does not share the same or corresponding technical feature because Group III is drawn to an antibody, which is a structurally and functionally different compound from the polypeptide and polynucleotides of Group I, and which can be made and used without those compounds. Lack of unity is shown because these compounds

lack a common utility which is based upon a common structural feature which has been identified as the basis for that common utility.

The claims of Group I include kits containing a polypeptide and an anti-thyrotropin antibody (claim 83). Thus, inventions I and III are also related as subcombinations disclosed as usable together in a single combination. At the time of the initial restriction requirement mailed 9/15/08, no pending claims included the single combination (kits comprising a polypeptide and an antibody). In the 10/7/08 response, new claim 83 to the single combination was added, but concurrently all claims to the subcombination of the antibody alone (without polypeptide) were canceled (claims 25-28). In the 4/17/09 response, Applicant has added new claim 94 directed to said subcombination (antibody alone without polypeptide). Thus, Applicant's amendments necessitate restriction between subcombinations usable together.

The subcombinations are distinct if they do not overlap in scope and are not obvious variants, and if it is shown that at least one subcombination is separately usable. In the instant case, the subcombination consisting of the protein alone (without the antibody) has separate utility such as treatment of hyperthyroidism. See MPEP § 806.05(d). The examiner has required restriction between subcombinations usable together. Where applicant elects a subcombination and claims thereto are subsequently found allowable, any claim(s) depending from or otherwise requiring all the limitations of the allowable subcombination will be examined for patentability in accordance with 37 CFR 1.104. See MPEP § 821.04(a). Applicant is advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Since Applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 86, 94 and 95 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (1/5/09).

The objection to the specification at pg 5 is *withdrawn in part* in view of Applicant's amendments to the specification. Specifically, the objections based on grounds (1) and (4) are withdrawn. The objections based on ground (2) and (3) are maintained (see below).

All rejections of claims 1, 4, 5, 55-58, 64, 66-69, 71, 76 and 84 are moot in view of Applicant's cancellation of these claims.

The rejection of claims 3, 61, 70, 72, 81-83 and 85 under 35 U.S.C. § 112, first paragraph at pg 6-12 for failing to provide enablement for the full scope of the claims is *withdrawn* in view of Applicant's amendments to the claims. However, please see below the new rejection of previously withdrawn claims 13, 37, 38, 61, 62, 73, 75, 79, 80, 89 and 93 under 35 U.S.C. § 112, first paragraph (enablement) necessitated by Applicant's amendments to the claims.

The rejection of claims 3, 61, 70, 72, 81-83 and 85 under 35 U.S.C. § 112, first paragraph at pg 12-14 for failing to comply with the written description requirement is *withdrawn* in view of Applicant's amendments to the claims. However, please see below the new rejection of previously withdrawn claims 13, 37, 38, 61, 62, 73, 75, 79, 80, 89 and 93 under 35 U.S.C. § 112, first paragraph (written description) necessitated by Applicant's amendments to the claims.

The rejection of claim 82 under 35 U.S.C. § 112, first paragraph at pg 12-14 for containing new matter is *withdrawn* in view of Applicant's amendments to the claim.

The rejection of claims 3, 61, 70, 72, 81-83 and 85 under 35 U.S.C. § 102(b) at pg 15-18 as being anticipated by Yang et al (2000) is *withdrawn* in view of Applicant's amendments to the claims.

The objection to claims 2, 59 and 60 at page 19 are withdrawn in view of Applicant's amendments to the claims.

Maintained Objections

Specification

The disclosure is objected to because of the following informalities:

(1) On page 40, it is stated that, "The sequence showed 99% homology with tiger (Panthera tigris) common alpha subunit (Genbank accession number AF354939)." However, this statement appears in Example 2, which is titled "Cloning and sequencing of feline thyrotropin β-subunit". Thus, it appears that the statement applies to Example 1 (concerning the cloning of the feline α-subunit) rather than Example 2.

Appropriate correction is required.

This objection was previously set forth as ground (2) of the objections to the specification at page 5 of the 1/5/09 Office Action. In the 4/17/09 response, Applicant includes a section (pg 11-12) addressing the other grounds of objection to the specification, but do not address this particular ground. Therefore, this ground of objection is maintained.

(2) On page 40, it is further stated that, "The feline TSHβ was different from canine TSHβ by 5 amino acids, equine TSHβ by 4 amino acids, and human TSHβ by 15 amino acids". However, Rayalam et al #2 (2006, Domestic Animal Endocrinology. 30: 203-217; cited on page 4 of the 1/3/07 IDS) teaches that the "projected amino acid homology of the secreted feline β-subunit was (amino acids, %): dog (111, 94%), cattle (107, 90.5%), horse (110, 93.2%) and human (104, 88%)(Fig. 6)" (pg 208). Thus, in contrast to the statement in the specification, feline TSHβ is different from canine TSHβ by 7 amino acids, equine TSHβ by 8 amino acids, and human TSHβ by 14 amino acids.

Appropriate correction is required.

This objection was previously set forth as ground (3) of the objection to the specification objection at page 5 of the 1/5/09 Office Action. In the 4/17/09 response, Applicant states that the objection is not understood and that it is "inappropriate" to "request that the specification be edited in view of information that published after the filing date of the present application" and that "doing so would potentially introduce new matter into the specification".

Applicant's arguments have been fully considered but are not found persuasive. It is not disputed that Rayalam et al (2006) was published after the filing date of the present application; however, said publication includes the instant Applicant (Duncan Ferguson) as an author and appears to describe the same invention (the cloned feline TSHβ gene and encoded protein). Furthermore, the feline TSHβ amino acid sequence shown in Figure 6 of Rayalam et al (pg 212) appears to be identical to the feline TSHβ amino acid sequence disclosed in the instant application (SEQ ID NO: 1). Furthermore, the dog, human, bovine and equine amino acid sequences shown in Figure 6 of Rayalam et al, and referred to on page 40 of the instant application, were all known in the prior art. Thus, the teachings of Rayalam et al (2006) provide objective evidence that the statements in the instant specification are not correct concerning the differences between the newly described feline and the previously known mammalian TSHβ amino acid sequences. If the statement at page 40 of the specification is not in error, Applicant should provide arguments and/or evidence showing why this statement is not in error. If the statement at page 40 of the specification is in error, Applicant should amend the specification to correct said error. It is noted that MPEP 2163.07 states, "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. *In re Odd*, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971)".

New objections and rejections necessitated by Applicant's amendment

Claim Objections

Claims 13, 73, 75, 79, 89 and 93 are objected to because of the following informalities:

Claims 13, 73, 75, 79, 89 and 93 recite a "thyrotropin α subunit" (no hyphen). However, claims 37, 62, 63 and 65 recite "thyrotropin α-subunit" (hyphen). Furthermore, the specification uses the term in its hyphenated form (e.g., page 1, line 23).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 37, 38, 61, 62, 73, 75, 79, 80, 89 and 93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(1) a yoked polypeptide, fusion polypeptide, or heterodimer comprising a first polypeptide comprising a thyrotropin β-subunit polypeptide comprising SEQ ID NO: 1 and a second polypeptide comprising a thyrotropin α-subunit comprising SEQ ID NO: 3;

(2) compositions and kits comprising (1),

does not reasonably provide enablement for

(3) a polypeptide comprising an isolated feline thyrotropin β-subunit polypeptide comprising SEQ ID NO: 1 and a second polypeptide comprising a thyrotropin α-subunit;

(4) compositions and kits comprising (2),

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a genus of isolated polypeptide variants comprising a feline thyrotropin β-subunit polypeptide of SEQ ID NO: 1 (without signal sequence) or SEQ ID NO: 2 (with signal sequence) and a feline thyrotropin α-subunit of SEQ ID NO: 3 (without signal sequence) or SEQ ID NO: 4 (with signal sequence). Thyrotropin is a mammalian heterodimeric protein consisting of two subunits (α and β). The β-subunit is

specific to thyrotropin; the α-subunit is shared with several other heterodimeric proteins. The specification also teaches a "yoked" fusion polypeptide comprising both subunits (SEQ ID NO: 5, without signal sequence; SEQ ID NO: 6, with signal sequences).

The specification teaches the following working examples in support of the claimed invention. Examples 1 and 2 (pg 39-40) teach the cloning and sequencing of the genes encoding feline thyrotropin α- and β-subunits (respectively). Example 3 (pg 41) teaches construction of the "yoked" fusion protein comprising the two subunits linked by a human chorionic gonadotropin C terminal peptide (CTP). Example 4 (pg 41-42) teaches baculovirus expression systems for the two subunits and the fusion protein. Example 5 (pg 43) describes expression of the two subunits and the fusion protein in three different cell systems. Examples 6 (pg 44) and 8(pg 46-48) describe immunological purification and detection of the proteins using an included FLAG epitope tag. Example 7 (pg 45-46) is labeled "prophetic example" and describes preparation of monoclonal antibodies against the fusion protein. Example 9 (pg 48-50) describes two assays to determine the biological activity of the fusion proteins. The first assay is a cAMP production assay using JP09 cells (CHO cells stably expressing the human TSH receptor). The specification reports that "[b]oth fTSH α/β heterodimer and yfTSH were biologically active in terms of cAMP production. fTSH heterodimer at 100 ng concentration produced 25 pmol/ml of cAMP where as yfTSH at the same concentration produced 70 pmol/ml. See the results presented in FIG. 6a" (pg 49). The second assay is a binding assay using the JP09 cells radioiodionated bovine TSH. The working examples presented in the specification are supported by two post-filing date publications (Rayalam et al #1, 2006. Domestic Animal Endocrinology. 30: 185-202; Rayalam et al #2, 2006. Domestic Animal Endocrinology. 30: 203-217; each cited on page 4 of the 1/3/07 IDS). Rayalam et al #1 teaches that "the heterodimeric and yoked forms of fTSH were able to inhibit the binding of ^{125}I-bTSH to the hTSH receptor in JP09 cells but with different affinities" (pg 195).

The teachings of the specification and relevant art provide enablement for polypeptides comprising the β-subunit of SEQ ID NO: 1. This genus broadly encompasses polypeptides consisting of the isolated β-subunit alone (with or without

signal sequence), which can be used to generate antibodies to the protein, or which can be used in conjunction with the isolated α-subunit in methods of treatment. This genus also includes fusion proteins comprising the β-subunit of SEQ ID NO: 1. The specification discloses a broad genus of fusion polypeptides comprising the β-subunit of SEQ ID NO: 1, including fusion partners that are for polypeptide purification (¶ 41 of the published application) or that are immunogenic carriers (¶ 59), or that are epitope tags for immunoaffinity detection (¶ 116). The broad scope of disclosed polypeptides provides enablement for the full scope for the claims "comprising SEQ ID NO: 1", including claims to "fusion proteins" comprising SEQ ID NO: 1. However, claims are also directed to a specific type of fusion protein or heterodimer comprising SEQ ID NO: 1; specifically, proteins comprising SEQ ID NO: 1 and a thyrotropin α-subunit.

The claims encompass non-naturally occurring variants of mammalian thyrotropin α-subunit polypeptides in which one or more amino acids of SEQ ID NO: 3 are substituted, deleted, and/or inserted. The specification envisions polypeptides that comprises an amino acid sequence with at least 80% similar to SEQ ID NO: 3 (the sequence of wildtype feline α-subunit without signal sequence). SEQ ID NO: 3 is 96 amino acids in length; thus the genus of variants with at least 80% similarity to SEQ ID NO: 3 includes up to 19 combined amino acid changes. SEQ ID NO: 4 is 120 amino acids in length and fully comprises SEQ ID NO: 2 and a signal sequence.

None of the claims include the limitation that the polypeptide variants exhibit a characteristic of the parent polypeptide of SEQ ID NO: 3, such as (when bound to a feline β-subunit) stimulating cAMP production in cells expressing the TSH receptor. Thus, both functional and non-functional mutated variants of SEQ ID NO: 3 are encompassed by the claims. Expected performance parameters of any of the possible variants of SEQ ID NO: 3 are limited to naturally-occurring sequences from other mammalian species that fall within the claimed genus. The specification has not provided a working example of the use of a non-naturally occurring variant of SEQ ID NO: 3, or sufficient guidance to enable one of skill in the art to make and use such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 3 could be modified to produce a polypeptide not identical to SEQ ID NO: 3 that retains a

characteristic of the parent polypeptide, e.g., (when bound to a feline β-subunit) stimulating cAMP production in cells expressing the TSH receptor.

Applicant has not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between SEQ ID NO: 3 and non-naturally occurring variants of said protein. If a variant of SEQ ID NO: 3 is to have a structure and function similar to SEQ ID NO: 3, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 3. Conversely, if a protein variant of SEQ ID NO: 3 need not have a disclosed property; the specification has failed to teach how to use such a variant.

Applicant does not identify any specific residues or regions of SEQ ID NO: 3 that are necessary for the activity of the protein. Furthermore, it is unpredictable whether or not the differences present in other naturally-occurring mammalian sequences can be used to predict changes that can be made to the feline sequence. A single amino acid change can drastically affect protein functionality if it occurs in a critical residue; thus, making a change based on another sequence may require additional compensatory changes elsewhere in the sequence. As noted in Ferrer-Costa (2007. J Mol Biol. 365: 249-256; cited previously), non-human sequences may contain residues that are disease-associated in humans, but which are not disease-associated in the non-human animal: these changes are explained by compensatory changes elsewhere in the protein (see Abstract).

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of

binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [Wells (1990); Ngo et al (1995); each cited previously]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000); Skolnick and Fetrow (2000) Doerks et al (1998); Brenner (1999); each cited previously].

To put the situation in perspective, the number of possible amino acid sequences that are 100 amino acids in length is 20^{100} (approx. 10^{130}). The number of possible amino acid sequences that are of a given % identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence (X = 19 for a polypeptide sequence), L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For example, for a 100 amino acid sequence that is at

least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6 x 10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is approximately 1.1 x 10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where n<<L. Using this formula to approximate N in this example gives a value of 1.7 x 10^{26}.

In the present case, the reference amino acid sequence SEQ ID NO: 3 is 96 amino acids long. A sequence that is at least 80% identical to SEQ ID NO: 3 tolerates up to 19 amino acid changes. Therefore, the total number of possible amino acid sequences that are at least 80% identical to SEQ ID NO: 3 is about 7.5 x 10^{44} ((19^{19} * 96^{19})/19!). Thus, while limiting the scope of potential sequences to those that are at least 80% identical to a reference sequence greatly reduces the number of potential sequences to test (as compared to having no structural limitation at all), it does not do so in any meaningful way. Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those which have the activity of SEQ ID NO: 3. Even considering a much narrower genus, such as those sequences at least 90% identical to SEQ ID NO: 3 (which tolerates up to 9 amino acid changes in any combination (0.90 x 118 = 86.4)), the total number of possible amino acid sequences is still about 6.1 x 10^{23} (19^9 * 96^9)/9!), which is more than a billion billions. Such a genus is still so vast that it would clearly require undue experimentation for the skilled artisan to make and test even a representative number of species from the genus.

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the

breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Ibid; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Thus, while the specification enables claims to a broad genus of proteins comprising SEQ ID NO: 1, narrower claims to proteins comprising SEQ ID NO: 1 and a thyrotropin α-subunit lack enablement because the specification fails to provide enablement for the genus of "thyrotropin α-subunit".

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 13, 37, 38, 61, 62, 73, 75, 79, 80, 89 and 93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant is claiming and what Applicant has possession of. The claims are genus claims directed to variant polypeptides; the genus is highly variant because a significant number of structural differences between members are permitted. The claims are directed to polypeptides comprising SEQ ID NO: 1 and a thyrotropin α-subunit. These

claims encompass polypeptides with α-subunits with any number of mutations with respect to SEQ ID NO: 3. The claims do not require that the polypeptides possess any particular conserved structure or function. The claims only require the claimed polypeptides comprise polypeptides sharing some structural similarity to the isolated polypeptide of SEQ ID NO: 3. Thus, the claims are drawn to a genus of polypeptides defined only by sequence similarity. The instant specification fails to describe the entire genus of polypeptides that are encompassed by each of these claims. From the specification, it is clear that Applicant has possession of polypeptides comprising isolated thyrotropin α-subunit polypeptides of SEQ ID NO: 3 (without signal sequence) and SEQ ID NO: 4 (with signal sequence). The specification fails to describe or teach any non-naturally occurring polypeptide which differs from the sequence of SEQ ID NO: 3 and retains the characteristics of the parent polypeptide. The claims, however, are not limited to a polypeptide of SEQ ID NO: 3.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative

teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a yoked polypeptide, fusion polypeptide, or heterodimer comprising a first polypeptide comprising a thyrotropin β-subunit polypeptide comprising SEQ ID NO: 1 and a second polypeptide comprising a thyrotropin α-subunit comprising SEQ ID NO: 3, and compositions and kits comprising such, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Conclusion

Claims 2, 3, 34-36, 59, 60, 70, 72, 81-83, 85, 87, 88, 90-92 and 96-98 are allowable.

Claims 9, 63, 65, 74, 77 and 78 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Bridget E Bunner/
Primary Examiner, Art Unit 1647